

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

55

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

To:

Pieraccioni, D.
ISTITUTO FARMACOLOGICO SERONO SPA
Via Casilina, 125
I-00176 Rome
ITALIE

Date of mailing
(day/month/year)

09.11.99

Applicant's or agent's file reference

WO/360/C

IMPORTANT NOTIFICATION

International application No.
PCT/EP98/06142

International filing date (day/month/year)
28/09/1998

Priority date (day/month/year)
29/09/1997

Applicant

APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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NL-2280 HV Rijswijk - Pays Bas
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Authorized officer

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference WO/360/C	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP98/06142	International filing date (day/month/year) 28/09/1998	Priority date (day/month/year) 29/09/1997
International Patent Classification (IPC) or national classification and IPC C12N15/19		
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 06/04/1999	Date of completion of this report 09.11.99
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Hix, R Telephone No. +31 70 340 3898 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/06142

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-14 as originally filed

Claims, No.:

1-12 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/06142

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-12
	No: Claims
Inventive step (IS)	Yes: Claims 1-12
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-12
	No: Claims

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/06142

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been taken into account;

DI : Genomics, vol. 40, pages 323-331, 1997, E. Van Coillie et al.

DII : Biochemical and Biophysical Research Communications, vol. 231, pages 726-730, 1997, E. Van Coillie et al.

DIII: J. Exp. Med. vol. 181, February 1995, pages 631-640, J-H. Gong et al.

1.) The prior art DIII discloses several truncated analogues of the C-C chemokine MCP-1 including 8-76, 9-76 and 10-76 which were not significantly active, however these analogues were antagonists of MCP-1 activity with the most potent being the 9-76 analogue and MCP-1 {3-76} being less potent.

2.) Amino-terminally truncated MCP-2, lacking the amino-terminal amino acid residues 1, 1-2, 1-3, 1-4 or 1-5 and having chemokine antagonistic activity are therefore novel according to Article 33{2} PCT.

3.) In view of the state of the art the problem may therefore be defined as the provision of alternative chemokines exhibiting antagonistic activity.

3.1} Although the DNA sequence encoding Human Monocyte Chemotactic Protein-2 {MCP-2} has been isolated and determined, DI and DII, there is neither indication nor suggestion in the state of the art that amino-truncated MCP-2 lacking the NH₂-terminal amino acids corresponding to amino acid residues 1-5 would exhibit chemokine antagonistic activity, as demonstrated in the application, page 11, line 30-31.

3.2} Thus subject-matter of the claims 1 to 12 appears to be neither anticipated nor suggested by the disclosures of the available prior art documents and as such are considered to satisfy the requirements of novelty and inventive step according to Articles 33{2} and {3} PCT.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D1 is not mentioned in the description.

Re Item VIII

Certain observations on the international application

1.) The abbreviation "{MCP-2}" must be defined as "Human Monocyte Chemotactic Protein-2" in Claim 1, to avoid ambiguity and for the sake of the clarity of the claims, according to Article 6 PCT.

2.) The description of the application, page 11 clearly illustrates that MCP-2 {6-76} still exhibits a chemokine antagonistic activity. However there is no evidence that a MCP-2 truncated at the NH₂-terminal and lacking any of the other amino-terminal amino acids would also still exhibit a chemokine antagonistic activity. The assertion of Claim 1 that amino-terminally truncated MCP-2, lacking the NH₂-terminal amino acids corresponding to amino acids 1, 1-2, 1-3 or 1-4 and still exhibiting a chemokine antagonistic activity appears to be purely speculative, not based on any technical facts or evidence and not supported by the description.

2.1) The subject-matter of Claim 1 is therefore considered to encompass subject-matter that is not demonstrated as involving an inventive step and not supported by the description according to Article 6 PCT.

2.2) The independent Claim 1 must define the subject-matter that is recognised as involving an inventive step, ie. the subject-matter of Claim 2 defining MCP-2{6-76}.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

PIERACCIOLI, Daniele
Istituto Farmacologico Serono
S.p.a.
Via Casilina, 125
I-00176 Rome
ITALIE

Date of mailing (day/month/year) 15 December 1999 (15.12.99)	
Applicant's or agent's file reference WO/360/C	IMPORTANT NOTIFICATION
International application No. PCT/EP98/06142	International filing date (day/month/year) 28 September 1998 (28.09.98)

1. The following indications appeared on record concerning:

☒ the applicant
 ☐ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address

APPLIED RESEARCH SYSTEMS ARS
HOLDING N.V.
John B. Gorsiraweg 14
Curacao
Netherlands Antilles

State of Nationality

NL

State of Residence

NL

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
 ☐ the name
 ☒ the address
 ☐ the nationality
 ☐ the residence

Name and Address

APPLIED RESEARCH SYSTEMS ARS
HOLDING N.V.
Pietermaai 15
Curacao
Netherlands Antilles

State of Nationality

NL

State of Residence

NL

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned
☐ the International Searching Authority
 ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority
 ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

G. Bähr

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference WO/360/C	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/EP 98/ 06142	International filing date (day/month/year) 28/09/1998	(Earliest) Priority Date (day/month/year) 29/09/1997
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☒ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 98/06142

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/19 C07K14/52 A61K38/19 A61K38/48 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	E. VAN COILLIE ET AL.: "The Human MCP-2 gene {SCYA8}: Cloning, Sequence Analysis, Tissue Expression and Assignment to the CC Chemokine Gene Contig on Chromosome 17q11.2" GENOMICS, vol. 40, 1 March 1997, pages 323-331, XP000197686 see the whole document --- -/--	1-12

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

28 January 1999

Date of mailing of the international search report

05/02/1999

Name and mailing address of the ISA

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Authorized officer

Hix, R

INTERNATIONAL SEARCH REPORT

International Application No

CT/EP 98/06142

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	E. VAN COILLIE ET AL.: "Human Monocyte Chemotactic Protein-2: cDNA cloning and regulated Expression of mRNA in Mesenchymal cells." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 231, 24 February 1997, pages 726-730, XP002044670 see the whole document ---	1-12
A	WO 97 25427 A (GENETICS INST) 17 July 1997 see the whole document ---	1-12
A	GONG J-H ET AL: "Antagonists of monocyte chemoattractant protein 1 identified by modification of functionally critical NH-2-terminal residues." JOURNAL OF EXPERIMENTAL MEDICINE 181 (2). 1995. 631-640. ISSN: 0022-1007, XP000644794 cited in the application see page 637, column 2 ---	1-12
A	GONG J-H ET AL: "RANTES and MCP -3 antagonists bind multiple chemokine receptors." JOURNAL OF BIOLOGICAL CHEMISTRY 271 (18). 1996. 10521-10527. ISSN: 0021-9258, XP002047804 cited in the application see table 1 ---	1-12
A	WEBER M ET AL: "Deletion of the NH-2-terminal residue converts monocyte chemotactic protein 1 from an activator of basophil mediator release to an eosinophil chemoattractant." JOURNAL OF EXPERIMENTAL MEDICINE 183 (2). 1996. 681-685. ISSN: 0022-1007, XP000609014 see the whole document ---	1-12
A	Y. ZHANG ET AL.: "A dominant negative inhibitor indicates that monocyte chemoattractant protein 1 functions as a dimer." MOLECULAR AND CELLULAR BIOLOGY, vol. 15, no. 9, September 1995, pages 4851-4855, XP000605358 see the whole document ---	1-12

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Y. ZHANG ET AL.: "MCP-1: Structure/activity analysis." METHODS: A COMPANION TO METHODS IN ENZYMOLGY, vol. 10, 1996, pages 93-103, XP000609055 see the whole document ----	1-12
A	ZHANG Y J ET AL: "Structure/activity analysis of human monocyte chemoattractant protein-1 (MCP -1) by mutagenesis. Identification of a mutated protein that inhibits MCP -1-mediated monocyte chemotaxis." THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 22, 3 June 1994, pages 15918-15924, XP002025858 see the whole document ----	1-12
A	M. BAGGIOLINI ET AL.: "Human Chemokines: An update." ANNUAL REVIEW OF IMMUNOLOGY, vol. 15, 1997, pages 675-705, XP002055737 cited in the application see page 689 - page 691 ----	1-12
A	J. VAN DAMME ET AL.: "Structural and functional identification of two human, tumor-derived monocyte chemotactic proteins (MCP-2 and MCP-3) belonging to the chemokine family" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 176, July 1992, pages 59-65, XP000673185 see the whole document -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/06142

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9725427 A	17-07-1997	AU 1532697 A	01-08-1997